Remarks

The December 23, 2008 Official Action and the references cited therein have been carefully reviewed. In view of the present amendments and following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At page 2 of the Official Action, the Examiner has rejected claims 9, 10, 12, 19, 36, 37, 52 under 35 U.S.C. §112, first paragraph as allegedly failing to satisfy the written description requirement.

Claims 9, 10, 12, 19, 21, 22, 24, 27, 36, 37, 46, 47, and 52 stand rejected under 35 U.S.C. §112, first paragraph. It is the Examiner's position that the specification fails to provide reasonable enablement for methods employing antisense mediated inhibition of p66shc in vivo.

Applicants respectfully submit that the claims as presently amended are in condition for allowance. Each of the above-noted rejections under 35 U.S.C. §112, first paragraph is, therefore, respectfully traversed.

THE CLAIMS AS AMENDED FULLY SATISFY THE REQUIREMENTS OF 35 U.S.C. §112, FIRST PARAGRAPH

A. Written Description

Claims 9, 10, 12, 19, 36, 37, 52 stand rejected under 35 U.S.C. §112, first paragraph as the specification allegedly fails to adequately describe the genus of agents encompassed by the claims. Applicants respectfully disagree. The skilled person having the sequence information provided in the specification before him or her would readily be able to obtain nucleic acid molecules, either antisense or siRNA which are effective to down modulate p66shc expression and use the same to reduce the expression of p66shc in target cells.

At page 4 of the Official Action, the Examiner acknowledges that the specification does describe an antisense nucleic acid which specifically hybridizes to a nucleotide sequence which encodes p66shc protein and is effective to down modulate expression of p66shc protein. In order to expedite prosecution, claims 9, 10, 12, 19, 36, 37 and 52 have been amended to recite this feature. Applicants reserve the right to file one or more continuing applications on any subject matter canceled in accordance with the present amendment.

It is submitted that the foregoing amendment obviates the rejection of the aforementioned claims based on inadequate written description. Accordingly, Applicants request the rejection be withdrawn.

B. Enablement

The Examiner has rejected claims 9, 10, 12, 19, 21, 22, 24, 27, 36, 37, 46, 47 and 52 asserting that undue experimentation would be required to practice the invention as claimed. Specifically, the Examiner contends that the specification fails to enable practice of the present method in vivo. Applicants respectfully and strenuously disagree.

At the outset, Applicants do not concur with the Examiner's assertion that the state of the antisense mediated gene inhibition is highly unpredictable. Indeed a search of the USPTO.gov database using the term ACLM/"antisense" reveals hundreds of issued patents directed to antisense molecules for down regulating expression of target genes of interest to treat pathological disorders. Notably, many of these patents are not limited to methods for in vitro administration and frequently exemplify the use of in vivo mouse models to demonstrate efficacy.

In further support of Applicant's position, listed below are several companies actively involved in developing antisense therapeutics for the treatment and prevention of a

wide variety of diseases which include viral infection, cancer, multiple sclerosis, cardiovascular disease, diabetes and inflammation.

1. Isis Pharmaceuticals (www.isispharm.com)
Isis Pharmaceuticals is the leading antisense company and "Vitravene" (fomivirsen) is the first antisense drug to achieve marketing clearance. Vitravene treats a condition called cytomegalovirus (CMV) retinitis in people with AIDS.

ISIS has 14 antisense drugs in clinical trials for indications including cancer, cardiovascular, inflammation, Multiple sclerosis and diabetes

2. Genta (www.genta.com)
Genta are currently developing "genesense" for cancer treatment and are in a phase II clinical trial (for Melanoma and CLL).

3. AVI BioPharma (www.avibio.com)
AVI BioPharma are in a phase I/II clinical trial with an antisense molecule for the prevention of restenosis. The also have another antisense molecule in phase I for Duchene Muscular Dystrophy.

4. OncoGenex (www.oncogenex.com)
Oncogenex has 5 antisense products in development (OGX-011, OGX-427, SN2310, CSP-9222 and OGX-22 3) all of which are undergoing clinical trials in cancer (OGX-011 is currently in Phase II/III)

5. Ester Neurosciences (www.amarincorp.com)
Ester Neurosciences are developing antisense molecules for the treatment of neurological disorders. They are currently in a Phase IIb with EN101 (orally available antisense) for the treatment of Myasthenia Gravis

6. Lorus Therapeutics (www.lorusthera.com)
Lorus Therapeutics have three antisense products in development and LOR 2040 is already undergoing clinical trials in cancer (AML).

Applicants have also performed a search of the PUBMED database using antisense as a search term. This search revealed no less than 28,635 hits. A listing of the first fifty abstracts identified is attached.

Finally, Applicants are also providing copies of several recent publications describing the use of efficacious

antisense molecules in vivo. See for example:

1. Cross-species comparison of in vivo PK/PD relationships for second-generation antisense oligonucleotides targeting apolipoprotein B-100
Yu RZ, Lemonidis KM, Graham MJ, Matson JE, Crooke RM, Tribble DL, Wedel MK, Levin AA, Geary RS. Biochem Pharmacol. 2008 Nov 14.

2. Regression of prostate cancer xenografts by RLIP76 depletion. Singhal SS, Roth C, Leake K, Singhal J, Yadav S, Awasthi S.
Biochem Pharmacol. 2008 Nov 25.

3. Antisense inhibition of ATM gene enhances the radiosensitivity of head and neck squamous cell carcinoma in mice Zou J, Qiao X, Ye H, Yang Y, Zheng X, Zhao H, Liu
J Exp Clin Cancer Res. 2008 Oct 26;27:56.

4. Enhanced therapeutic effects for human pancreatic cancer by application K-ras and IGF-IR antisenseoligodeoxynucleotides Shen YM, Yang XC, Yang C, Shen JK.
World J Gastroenterol. 2008 Sep 7;14(33):5176-85

5. Matrix metalloproteinase-9 Inhibition Down-RegulatesRadiation-Induced Nuclear Factor-KB Activity Leading to Apoptosis in BreastTumors Kunigal S, Lakka SS, Joseph P, Estes N, Rao JS.
Clin Cancer Res. 2008 Jun 1;14(11):3617-26.

6. Survivin Antisense Oligonucleotides Effectively Radiosensitize Colorectal Cancer Cells in both Tissue Culture and Murine Xenograft Models Rödel F, Frey B, Leitmann W, Capalbo G, Weiss C, Rödel C.
Int J Radiat Oncol Biol Phys. 2008 May 1;71(1):247-55.

In view of all the foregoing, Applicants take exception to the Examiner's assertion that the present claims are not fully enabled by the disclosure in the specification. Indeed, once the antisense molecule for the target is identified, routine methods are available for administering the same to a subject in vivo as are methods for assessing the subject for a reduction in symptoms associated with arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infarction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer's, cancers, and vascular

complications of diabetes. The Examiner has acknowledged that Applicants have described an antisense sequence which is effective to down modulate production of p66shc protein. Administration of the molecule the invention in vivo is well within the purview of the skilled person without resort to undue experimentation. In In re Wands, 8 USPQ2d 1400 (1988) cited by the Examiner, the Federal Circuit Court of Appeals held that engaging in experimentation to practice a claimed invention does not render the disclosure non-enabling as long as the experimentation required is not "undue". The Court stated that: "The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the present case, the experimentation necessary is merely routine and is inherent in the nature of the art. Therefore, there is no undue burden of experimentation. The level of skill in the art of antisense administration is high as exemplified by the many citations provided herein, and the required techniques for administration of the same are familiar to those skilled in this art area. Indeed, the endpoints to be assessed for efficacy, i.e., the metabolic changes described in Figure 9 and means for assessing the same are all disclosed in the specification. In view of all the foregoing, it is respectfully submitted that the specification wholly enables practice of the full scope of the currently claimed methods. Nothing more is required under 35 U.S.C. §112, first paragraph. Accordingly, Applicants request the rejection be withdrawn.

CONCLUSION

It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

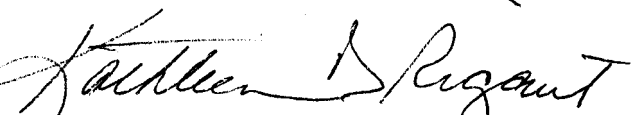
In view of the present claim amendments, and the foregoing remarks, Applicants request that the rejections set forth in the December 23, 2008 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

In the event a fee is required or an overpayment is made, the Commissioner is authorized to charge or credit the deposit account of the undersigned, Account No. 04-1406.

Early and favorable action on the present application is earnestly solicited.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 
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